**Triple Whammy** – ‘three simultaneous deleterious blows with compounded effect’. The combination of medicines above can result in significant harm. Used individually or combined, these three types of medicines are involved in more than half of all reported iatrogenic acute renal failure cases.

**AVOID THIS COMBINATION OF MEDICINES IF POSSIBLE**

The combination of these medicines should be avoided particularly if people have risk factors for renal failure. The simplest way to avoid the triple whammy is by avoiding NSAIDs. When an ACE inhibitor/ARB with a diuretic is prescribed, highlight in the patient’s notes or medication allergy/alerts section to avoid NSAIDs in future and advise them not to purchase NSAIDs themselves.

Although the focus of adverse effects from NSAIDs is usually on the gastrointestinal consequences, there are other risks such as the development of chronic heart failure and acute kidney injury. Older adults and people with co-morbidities such as heart failure or severe liver disease or dehydration from acute illness have an increased risk of acute kidney injury. (AKI)

ACE inhibitors and NSAIDs adversely affect renal blood flow and diuretics have the potential to cause dehydration. Each of these medicines affects renal function, either directly or indirectly; a ‘double whammy’ can be harmful if people already have risk factors for AKI. Further, NSAIDs antagonise beneficial antihypertensive effects of ACE inhibitors and diuretics in people with heart failure. If NSAIDs are unavoidable, use at the lowest dose for the shortest duration possible; check renal function at baseline and periodically during treatment.

**Monitoring Recommendations**

<table>
<thead>
<tr>
<th>Medicine type</th>
<th>Interaction with NSAIDs</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>↓ Antihypertensive effect</td>
<td>Monitor blood pressure, weight and renal function</td>
</tr>
<tr>
<td>Diuretics</td>
<td>↓ Diuretic effect</td>
<td>Monitor blood pressure, weight and renal function</td>
</tr>
<tr>
<td>ACE inhibitors + diuretics</td>
<td>↑ Risk of acute kidney injury</td>
<td>AVOID combination with NSAIDs if possible</td>
</tr>
</tbody>
</table>

The Centre for Adverse Reaction Monitoring (CARM) in New Zealand received 119 reports of renal adverse reactions associated with NSAID use from January 2000 to December 2012. This included four deaths, and 12 cases that were considered life-threatening. Most of the reports were in adults over 50 years of age. The ‘Triple Whammy’ was described in four reports. CARM encourage all healthcare professionals to report suspected adverse reactions to NSAIDs.

Cases of acute kidney injury attributed to NSAIDs often involve people taking the maximum or greater than the maximum recommended daily dose.

**BE AWARE OF THE RISK FACTORS FOR ACUTE KIDNEY INJURY**

Dehydration from vomiting, diarrhoea and sepsis can be a trigger for acute kidney injury; minor illness can place susceptible people at risk if they are taking ‘Whammy’ combinations. Advise people to avoid hypovolaemia (drink plenty of water) and to seek medical advice if they become acutely unwell.
Prescribing NSAIDs in older adults especially if they are dehydrated. Note: This does not include over the counter NSAIDs.

The Health Quality and Safety Commission Atlas of Healthcare Variation revealed that 20,000 people in New Zealand 65 and over were dispensed the triple whammy in 2017. Rates were significantly higher in younger Māori and Pacific people.

ADVISE PEOPLE WHO ARE PRESCRIBED ACE INHIBITORS AND DIURETICS NOT TO ‘SELF-MEDICATE’ WITH NSAIDS

Combination ACE-inhibitor or angiotensin II receptor antagonists with diuretics (eg Accuretic®) are useful products, but always advise people to avoid self-medicating with ‘over-the-counter’ NSAIDs. This combination has been associated with a 31% increased rate of acute kidney injury; the risk of injury doubles in the first 30 days of NSAID use.

There remains a high prevalence of NSAID use among people with relative contraindications, such as people with chronic conditions or who are at risk of drug-related adverse events. A study examining NSAID use in people with identified contraindications, found that 22% of them purchased their NSAIDs exclusively over-the-counter. Of those, 1 in 5 did not report the use of NSAIDs to clinical staff; this may reflect that they consider these medications to be insignificant. Although some people may be unaware of the risks of NSAIDs, others may choose these medicines because they offer relief of pain that is not achieved through other means.

REFERENCES
10. Lobo K, Shenfield G. Drug combinations and impaired renal function. [continued]

ACKNOWLEDGEMENTS
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For further information on other high-risk medicines visit our website at: www.saferx.co.nz